REMARKS

I. Claim Status

Claims 1, 4, and 7-10 are currently pending and stand rejected. Claims 1, 4, and 7-10 have been amended herein to delete "or hydrate" and/or to include "a prodrug." Those amendments are supported throughout the specification as originally filed. Accordingly, no new matter is added.

II. Enablement Rejection

The Examiner rejected claims 1, 4, and 7-10 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement, stating that the specification "does not reasonably provide enablement for a hydrate of the compound in the instant claims." Non-final Office Action dated March 23, 2009, pp. 2-3 ("Office Action"). Without in any way conceding the propriety of this rejection and solely in an effort to expedite prosecution, the claim 1, 7, and 9 have been amended to delete "or hydrate." This rejection is thus rendered moot because the Examiner expressly states that the present specification is enabling for "a pharmaceutically acceptable salt of the compound." Office Action at 2.

III. Double Patenting Rejections

The Examiner rejected claims 1, 4, and 7-10 over claims 1, 5, 6, 8, 14, and 16-24 of U.S. Patent No. 6,313,311 to Karjalainen et al. ("the '311 patent") on the ground of nonstatutory obviousness-type double patenting. Office Action at 8. Applicants respectfully traverse this rejection.

In support of this rejection, the Office states that "[a]lthough the claims are not identical, they are not patentably distinct from each other because the instant claimed compound is ***generically described in the patent***." Office Action at 8-9 (emphasis

added). Applicants respectfully point out that the Office may not use the specification as prior art. *See* M.P.E.P. § 804 ("When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent ***may not be used as prior art.*** *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992) (emphasis added)).

Consequently, the Office may only consider the claims of the '311 patent. Those claims do not encompass the presently claimed prodrugs or methods of using said prodrugs. In fact, the presently claimed prodrugs "4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1*H*-imidazole or a pharmaceutically acceptable salt thereof" (claim 1) do not even fall within the broad genus claim of the '311 patent because R_6, R_7, and R_8 cannot be ester groups, let alone the pivaloyl group presently claimed. Thus, this is not a situation of "[t]he indiscriminate selection of 'some' among 'many.'" Office Action at 9. And, the claims of the '311 patent do not provide any reason or motivation to one of ordinary skill in the art to arrive at the presently pending claims. As a result, this rejection should be withdrawn.

The Examiner rejected claims 7 and 8 over claims 15, 16, 19-24, and 27-32 of U.S. Patent Application No. 11/641,953 ("the '953 application") on the ground of nonstatutory obviousness-type double patenting. Office Action at 10. Applicants respectfully traverse this rejection.

Here again, the claims used to reject the present claims, i.e., 15, 16, 19-24, and 27-32 of the '953 application do not "generically embrace" the presently claimed compounds because there is no possibility for an ester on the phenyl ring, let alone in

the presently claimed 6-position. Thus, this is likewise not a situation where there is an indiscriminate selection of "some" among "many." *See* Office Action at 10. The claims of the '953 application provide no suggestion or motivation to one of skill in the art to modify the -OH group of the phenyl ring to arrive at the specifically substituted pivaloyl group of the presently claimed prodrugs, methods of using the same, and pharmaceutical compositions comprising the same. As a result, this rejection should be withdrawn.

IV. 35 U.S.C. § 103(a) Rejection

The Examiner rejected claims 1, 4, and 7-10 under 35 U.S.C. § 103(a) as allegedly obvious over WO 97/12874 to Karjalainen ("WO '874") and the '311 patent each taken alone or in view of WO 01/051472 ("WO '472"), Bundgaard, H. "Novel chemical approaches in prodrug design," *Drugs of the Future* (1991) 16(5):443-458 ("Bundgaard I"), U.S. Patent No. 4,673,679 to Aungst et al. ("Aungst"), and Krogsgaard-Bundgaard, H., "Chapter 5. Design and Application of Prodrugs" in *A Textbook of Drug Design and Development* (1991), Harwood Academic Publishers, Philadelphia, pp. 112-191 ("Bundgaard II"). Office Action at 12.[1] Applicants respectfully traverse this rejection.

As an initial matter, the Office has previously rejected the presently pending claims over the '311 patent (as WO '874) alone and in view of WO '472. Final Office Action dated June 11, 2008, p. 3. Applicants maintain their position, that no *prima facie* case of obviousness over the '311 patent alone or in view of WO '472 has been

[1] The '311 patent is a § 371 continuation of the International Application that published as WO '874. The specifications of the two documents are the same. Accordingly, Applicants refer to only the '311 patent herein.

established and refer the Examiner to Applicants' comments in their Appeal Brief dated December 10, 2008. For the reasons articulated therein, no *prima facie* case over the '311 patent alone or in view of WO '472 has been established.

The arguments submitted in Applicants' Appeal Brief were directed to the claims pending before the October 10, 2008, Amendment, comprising various ester groups at position 6 (claim 1 before Oct. 10, 2008 amendment), whereas the presently pending claims are directed to only the pivaloyl group at that position (current claim 1). Thus, the arguments presented in the Appeal Brief are even stronger in view of the presently pending claims because the '311 patent and WO '472 are wholly silent with respect to such a group. In view of the Federal Circuit's reasoning in *Takeda Chem. Ind., Ltd. v. Alphapharm PTY., Ltd.* 492 F.3d 1350, 1357 (Fed. Cir. 2007) that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound," neither the '311 patent nor WO '472 provide the requisite reason to modify their compounds to reach the presently pending claims.[2]

Aungst, Bundgaard I, and Bundgaard II fail to compensate for the deficiencies of the '311 patent and WO '472. In fact, these documents actually teach away from their combination with WO '472. The Office relies on these documents to show the "advantages of ester prodrugs and why one skilled in the art would be motivated to prepare such ester prodrugs." Office Action at 14. As defined in the present

[2] Applicants also respectfully point out that the presently claimed compounds are not claimed in the '311 patent generically as the Examiner alleges on p. 13 of the Office Action.

specification (p. 1) and in Bundgaard I (p. 443) and II (p. 114) a "pro-drug is a pharmacologically inactive derivative of a parent drug molecule . . . ." In contrast, WO '472 contemplates that any ester derivatives of the -OH groups of the compounds disclosed therein "retain the pharmacological properties of the free form." WO '472 at 8. In other words, WO '472 does not consider any potential ester derivatives to be prodrugs: it simply contemplates other active compounds falling within the scope of its invention. Consequently, Aungst, Bundgaard I and Bundgaard II cannot be combined with WO '472 because their respective disclosures teach away from one another. *See* M.P.E.P. § 2145.

In addition, Aungst, and Bundgaard I and II fail to provide the requisite reason dictated by *Takeda* to modify the compounds of the '311 patent to arrive at the presently claimed compounds and the use thereof, i.e., none of these documents teaches modifying the compounds of the '311 patent to have a pivaloyl group at the 6-position. Indeed, neither of the Bundgaard documents even discloses pivaloyl group as a potentially useful prodrug ester.

And, Aungst discloses that the pivaloyl group is less effective as a prodrug group on a 3-hydroxymorphinan analgesic, agoninst-antagonist, or narcotic antagonist (compounds unrelated to those presently claimed). Specifically, in Table 1 (col. 11) of Aungst, the pivaloyl group resulted in less than 10% hydrolysis after 24 hours in human plasma. As discussed in Bundgaard I, a prodrug "requires spontaneous or enzymatic transformation in the body in order to release the active drug." p. 443. Less than 10% hydrolysis in 24 hours indicates that the pivaloyl group is not satisfactorily cleaved to release the active pharmaceutical ingredient. In addition, the pivalates of nalbuphine,

naloxone, and naltrexone are each less bioavailable than their parent compounds, another unsatisfactory quality of prodrugs. *See* Aungst Table 7. These results contradict the teachings of Bundgaard I because "[p]rodrugs are designed to overcome pharmaceutically and/or pharmocokinetically based problems [e.g., bioavailability] associated with the parent drug molecule that would otherwise limit the clinical usefulness of the drug." p. 443; *see also* Bundgaard II at 114.

Moreover, Aungst and the Bundgaard documents highlight the unpredictability of selecting a suitable prodrug. In particular, no one ester—or other functional group for that matter—is universally suitable for all potential prodrug applications. For example, Bundgaard I explains that "many aliphatic or aromatic esters are not sufficiently labile *in vivo* to ensure a sufficiently high rate and extent of prodrug conversion." p. 444. In a specific example, the simple alkyl and aryl esters of penicillin are not hydrolyzed to the active free penicillin *in vivo*, and as a result have no pharmaceutical value. *Id.*

As mentioned above, the pivaloyl group of Aungst is far less labile than, for example, the dodecanoyl group (hydrolyzed in 0.9 hr). Aungst, Table 1, entry 3. And, there does not appear to be any predictable trend for the different activities disclosed for the various ester moieties in Aungst. Thus, in view of Aungst and the Bundgaard documents, one of ordinary skill in the art would not have expected success by modifying the compounds of the '311 patent to arrive at the presently pending claims in view of the unpredictability in the prodrug art. For at least the reasons discussed herein, this rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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